Contents lists available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

Glucose tolerance, insulin resistance and insulin secretion in young south Indian adults: Relationships to parental size, neonatal size and childhood body mass index

Palany Raghupathy [a,*], *Belavendra Antonisamy* [b], *Finney S. Geethanjali* [c], *Julia Saperia* [d], *Samantha D. Leary* [d], *G. Priya* [b], *Joseph Richard* [b], *David J.P. Barker* [d], *Caroline H.D. Fall* [d]

[a] *Departments of Child Health, Christian Medical College, Vellore, 632004, India*
[b] *Departments of Biostatistics, Christian Medical College, Vellore, 632004, India*
[c] *Departments of Clinical Biochemistry, Christian Medical College, Vellore, 632004, India*
[d] *MRC Epidemiology Resource Centre, University of Southampton, Southampton General Hospital, SO16 6YD, UK*

ARTICLE INFO

Article history:
Received 27 March 2009
Received in revised form
26 October 2009
Accepted 24 November 2009

Keywords:
Type 2 diabetes mellitus
Impaired glucose tolerance
Insulin resistance
Childhood body mass index
Young adulthood

ABSTRACT

Objective: To study the relationship of newborn size and post-natal growth to glucose intolerance in south Indian adults.

Research design and methods: 2218 men and women (mean age 28 years) were studied from a population-based birth cohort born in a large town and adjacent rural villages. The prevalence of adult diabetes mellitus [DM] and impaired glucose tolerance [IGT], and insulin resistance and insulin secretion (calculated) were examined in relation to BMI and height at birth, and in infancy, childhood and adolescence and changes in BMI and height between these stages.

Results: Sixty-two (2.8%) subjects had Type 2 diabetes (DM) and 362 (16.3%) had impaired glucose tolerance (IGT). IGT and DM combined (IGT/DM) and insulin resistance were associated with low childhood body mass index (BMI) ($p < 0.001$ for both) and above-average BMI gain between childhood or adolescence and adult life ($p < 0.001$ for both). There were no direct associations between birthweight or infant size and IGT/DM; however, after adjusting for adult BMI, lower birthweight was associated with an increased risk.

Conclusions: The occurrence of IGT and Type 2 DM is associated with thinness at birth and in childhood followed by accelerated BMI gain through adolescence.

1. Introduction

By 2030, more than 75% of the world's 366 million adults with diabetes will live in developing countries [1]. India will have approximately 79 million, with the highest prevalence in cities. Recent studies show that diabetes is increasing even in rural areas and that the pre-diabetic condition, impaired glucose tolerance (IGT), occurs as frequently as in urban populations, predicting a high future burden of disease [2,3].

Studies in high-income white Caucasian populations suggest that small size at birth or during infancy, and accelerated BMI gain during childhood, are risk factors for diabetes [4,5]. These findings have recently been confirmed in a study of young adults in the city of Delhi, India [6]. There is no relevant published data from rural populations, which tend to

* *Corresponding author at*: No. 39, 6th Cross Road, 35th Main, KAS Officers' Colony, BTM, Layout II Stage, Bangalore 560 068, India. Tel.: +91 80 2668 7333; fax: +91 80 2244 2700.
E-mail address: p.raghupathy@gmail.com (P. Raghupathy).
0168-8227/$ – see front matter © 2009 Published by Elsevier Ireland Ltd.
doi:10.1016/j.diabres.2009.11.015

have a lower prevalence of Type 2 diabetes, lower birthweight and rates of childhood weight gain, and lower adult BMI than urban populations.

We studied glucose tolerance and insulin profiles, and their relationship to newborn size and infant, childhood and adolescent growth, in men and women aged 26–32 years who were born in rural and urban south India. The prevalence of IGT and diabetes in this cohort, and associations with adult lifestyle factors, were presented earlier [2].

2. Methods

2.1. The cohort

The subjects came from an original cohort of people born during 1969–1973 in North Arcot (now Vellore) district in Tamilnadu State [7–9]. When the cohort was established, 24 wards in Vellore town representing different socio-economic strata, and 25 of 41 contiguous villages from the nearby Kizhvazhithunaiyankuppam rural community [8,9] were selected. A total of 20,626 married women of reproductive age (8998 urban, 11,628 rural) were recruited. Their own and their husbands' weight and height were recorded, and they were visited regularly by health workers to record menstrual dates and follow-up pregnancies. Of 14,147 completed pregnancies, there were 10,691 single live births, 97 multiple births and 3359 fetal deaths. Many mothers (mainly primiparae) traditionally returned to their parents' homes for delivery, and hence 47% of babies were born outside the study area and were unavailable for newborn examination; the remainder were measured (weight and length) within 120 h of delivery by trained personnel. These measurements were repeated during follow-up phases in infancy (1–3 months), childhood (6–8 years) and adolescence (10–15 years). A detailed description of the cohort is presented elsewhere [10].

2.2. Present study

All subjects who were singleton births, and whose parental and birth measurements were available ($n = 4092$) were considered eligible. Those still living within the study area, or in nearby villages, towns or cities ($n = 2572$) were traced by health workers. The study was carried out between 1999 and 2002.

2.3. Questionnaire

A questionnaire was administered at home to obtain information on family history of diabetes in a first degree relative, parity (women only), occupation, education, tobacco and alcohol use, physical activity and socio-economic status. Complete details regarding the questionnaire data were presented earlier [2]. Occupation was defined in 7 groups from unemployed to professional level, and education in 7 groups from no schooling to a professional qualification. Subjects were defined as current tobacco users or non-users, including all forms of tobacco (smoked, chewed or snuff). Frequency and quantity of consumption of beer, wine and spirits were converted into units of alcohol per week. A score was derived as a summary estimate of daily physical activity [2]. Socio-economic status was assessed on possession of up to 15 household items (gas-stove, bicycle, home electric connection, fan, food processor, radio, television, cable television, electric wet grinder, telephone, air cooler, washing machine, motorized 2-wheeled vehicle, air conditioner, computer, car).

2.4. Clinic visits

Subjects attended the clinic after an overnight fast. Urban subjects came to the main hospital in Vellore, and rural subjects to the Rural Unit for Health and Social Affairs (RUHSA). Pregnant women attended 6–10 months after delivery. Weight, waist and hip circumferences, and height were recorded by one of two physicians. Fasting venous blood samples were obtained for plasma glucose and insulin concentrations. Subjects then had a 75 g anhydrous glucose load, and blood samples were collected 30 and 120 min later for plasma glucose and insulin concentrations. Blood samples from the rural clinic were transported on ice to the main hospital laboratory and centrifuged within 3 h of collection. Insulin samples were preserved at -80° C and analysed within 2 weeks.

2.5. Biochemical estimations

Plasma glucose was measured using glucose oxidase/peroxidase enzymatic methods by Hitachi 911 autoanalyser. Plasma insulin was measured by immunoradiometric assay (Coat-a-count kits, Diagnostic Products Corporation, USA). Roche Precinorm and Precipath controls were used for internal quality assessment of glucose assays and BioRad immunoassay controls for insulin. Intra- and inter-assay coefficients of variation for insulin estimations were 8.0–14.5% and 8.2–13.0%, respectively.

2.6. Definitions

Impaired glucose tolerance (IGT) was defined as a fasting plasma glucose <7.0 mmol/l and a 120-min value ≥ 7.8 and <11.1 mmol/l, and diabetes as a fasting glucose concentration ≥ 7.0 mmol/l or a 120-min concentration ≥ 11.1 mmol/l [11]. Insulin resistance was calculated using the HOMA equation [12]. The 30-min insulin increment (30-min insulin minus fasting insulin)/30-min glucose) was used as a measure of insulin secretion [13,14].

2.7. Statistical methods

The outcomes we considered were IGT and DM combined (IGT/DM), insulin resistance and insulin increment. Insulin resistance and increment had skewed distributions and were transformed to normality using the normal scores method. The effects of parental BMI and height, and the subjects' BMI and height in early life (birth, infancy, childhood and adolescence) on adult outcomes were examined using tabulation of means (checking for non-linear relationships) and by linear and logistic regression, using variables as continuous where appropriate, and adjusting for other variables as stated. By convention, ponderal index at birth

(weight in kg/length in metres^3) was used, rather than BMI. Because the childhood measurements were recorded in phases, and therefore at slightly differing ages for different children, body measurements in early life were age-adjusted and converted into within-cohort age- and sex-specific Z-scores [(subject mean − cohort mean)/cohort SD]. The cohort mean and SD were derived from all 4092 individuals with complete birth and parental measurements. Infant data were included if there was at least one measurement between 1 and 3 months, and the latest available time point used. Childhood data were included if there was at least one measurement between 6 and 8 years, and the average Z-score used if there was more than one measurement. Adolescent data were included if there was at least one measurement between 10 and 14 years, the Z-score for the age closest to 12 years being selected. The main analysis used all available data at each timepoint; the analysis was also repeated using the sub-set of participants having data for all timepoints (parental size, and birth, infant, childhood and adolescent measurements).

Participants gave their written informed consent. The study was approved by the Institutional Research Ethics Committees.

3. Results

Of 2572 men and women traced, 2218 (86%) participated in the study. The majority were Hindus (94%); Muslims and Christians were 5 and 1%. Their mean (SD) age was 28.3 (1.1) years and median BMI was 20.0 kg/m^2. Urban-born subjects were heavier and taller than rural-born children at all ages, except during infancy when they were lighter and thinner (Table 1).

3.1. *Differences between subjects studied and not studied*

Comparison between the 2218 subjects studied and the remainder of the 4092 eligible subjects showed no significant differences in parental size or in childhood and adolescent measurements. Birth and infant measurements of individuals studied vs. not studied were: birthweight (2813 g vs. 2,762 g; $p = 0.002$), birth length (48.1 cm vs. 47.8 cm, $p = 0.002$), 3-month weight (4,859 g vs. 4,704 g, $p < 0.001$) and 3-month length (57.9 cm vs. 57.7 cm, $p = 0.2$).

3.2. *Relationship of outcomes to adult factors*

Altogether, 34 men (2.9%) and 28 women (2.7%) had diabetes, of whom 8 were already known to have diabetes (one requiring insulin). A further 172 men (14.8%) and 190 women (18.0%) had IGT. As previously described [2], the following adult factors were associated with an increased risk of IGT and diabetes or higher insulin resistance: urban residence, a family history of diabetes, higher BMI and waist/hip ratio, more household possessions, higher education level, higher alcohol intake, non-use of tobacco and less physical activity. Insulin increment was lower in men with higher alcohol consumption [2]. Analyses of associations of early life variables with adult outcomes were adjusted for age and sex only, and then further adjusted for these adult factors. The prevalence of IGT and diabetes was higher in urban-born than rural-born subjects (Table 1). These differences were not statistically significant after adjusting for current place of residence and the other adult factors. Insulin resistance was positively associated with adult height ($p < 0.001$ unadjusted and $p = 0.001$ adjusted for adult lifestyle factors); IGT/DM and insulin increment were unrelated to adult height. Insulin resistance was highest in subjects with Type 2 DM (median = 2.5), lower in those with IGT (1.1) and lowest in those with normal glucose tolerance (1.0). Insulin increment was lowest in subjects with Type 2 DM (median = 8.3), higher in those with IGT (12.8) and highest in those with normal glucose tolerance (13.5). Insulin resistance and increment were positively correlated ($r = 0.17$, $p < 0.001$).

3.2.1. *Diabetes and IGT and measurements in earlier life*

All associations reported below between size in early life and adult outcomes were similar in rural-born and urban-born subjects.

3.3. *Parental BMI and height*

IGT/DM was associated with shorter maternal height ($p = 0.02$) (Table 2). The prevalence was 21.4% in subjects with mothers in the lowest fifth of height (<146 cm) compared with 16.5% for the highest fifth (>156 cm). IGT/DM was not directly related to parental BMI; however, after adjustment for adult BMI and lifestyle factors, subjects whose mother or father had a lower BMI were more likely to have IGT/DM (Table 2).

3.4. *Size at birth and in infancy*

There were no direct associations between size at birth or in infancy and adult IGT/DM (Table 2). After adjustment for adult BMI and lifestyle factors, lower birthweight and lower ponderal index at birth were associated with an increased risk of IGT/DM (Table 2). These findings were not changed if birth measurements were adjusted for gestational age.

3.5. *Childhood and adolescence*

Subjects with a lower childhood BMI had an increased risk of IGT/DM (Table 2 and Fig. 1). An increase in BMI Z-score from birth, infancy, childhood or adolescence to adult life was associated with an increased risk of IGT/DM (Table 2). The highest risk was in subjects in the lowest third of early BMI and the highest third of adult BMI (shown for childhood and adult BMI in Table 3). There were, however, no statistically significant interactions between early-life BMI (any timepoint) and adult BMI in relation to IGT/DM. There were no associations between childhood or adolescent height and IGT/DM.

3.6. *Limiting the sample to subjects with data at all timepoints*

We re-analysed the data, limiting the sample to men and women with data at all timepoints (data for both parents and measurements at birth, infancy, childhood and adolescence, N = 1108). All the statistically significant associations reported

Table 1 – Parental measurements, anthropometry in early life and adulthood, and adult biochemistry and IGT/DM prevalence according to place of birth.

	N	Men		Women		$p^{\dagger}$	$p^{\dagger\dagger}$
		Rural max. no. 799	Urban max. no. 362	Rural max. no. 766	Urban max. no. 291		
Parents							
Mother							
Height (cm)	2218	151.3 (5.5)	150.3 (6.5)	151.1 (5.1)	150.1 (6.2)	0.5	<0.001
BMI (kg/m^2)	2218	18.4 (2.0)	19.5 (3.7)	18.6 (2.1)	19.2 (3.4)	0.8	<0.001
Father							
Height (cm)	2218	162.4 (5.7)	162.1 (8.1)	162.4 (5.9)	161.7 (7.9)	0.7	0.1
BMI (kg/m^2)	2217	19.3 (2.2)	20.6 (3.6)	19.4 (2.2)	20.9 (3.6)	0.5	<0.001
Birth							
Weight (g)	2115	2787 (462)	2906 (488)	2719 (436)	2825 (509)	<0.001	<0.001
Length (cm)	2192	48.1 (2.6)	49.0 (2.9)	47.5 (2.5)	48.5 (2.6)	<0.001	<0.001
Ponderal index	2103	25.3 (4.2)	25.0 (4.9)	25.5 (4.1)	25.1 (4.7)	0.4	0.1
Gestation (weeks)	1825	38.6 (2.7)	38.7 (2.7)	38.6 (2.9)	38.9 (2.7)	0.7	0.2
Infancy[b]							
3 months							
Weight (kg)	1186	5.1 (0.8)	4.8 (0.9)	4.8 (0.7)	4.5 (0.7)	<0.001	<0.001
Height (cm)	1107	58.1 (3.0)	59.2 (3.2)	57.4 (3.0)	57.8 (2.9)	<0.001	<0.001
BMI (kg/m^2)	1075	15.0 (1.9)	13.9 (2.2)	14.5 (1.7)	13.5 (1.9)	<0.001	<0.001
Childhood[b]							
7 years							
Weight (kg)	1375	16.4 (2.1)	16.8 (2.3)	16.3 (2.2)	16.7 (2.4)	0.2	0.005
Height (cm)	1373	108.2 (5.2)	110.0 (6.0)	107.6 (5.8)	109.4 (6.1)	0.04	<0.001
BMI (kg/m^2)	1373	14.0 (1.4)	13.8 (1.1)	14.1 (1.5)	13.9 (1.3)	0.5	0.04
Adolescence[b]							
12 years							
Weight (kg)	1199	25.0 (3.1)	25.7 (3.7)	25.7 (3.8)	27.3 (4.6)	<0.001	<0.001
Height (cm)	1200	132.1 (6.0)	134.0 (7.5)	133.0 (7.0)	135.2 (6.9)	0.01	<0.001
BMI (kg/m^2)	1199	14.3 (1.1)	14.2 (1.2)	14.4 (1.2)	14.9 (1.5)	<0.001	0.01
Adulthood							
Weight[a] (kg)	2210	54.2 (48.0, 62.0)	59.4 (50.5, 69.0)	46.0 (40.5, 52.9)	53.4 (45.4, 61.5)	<0.001	<0.001
Height (cm)	2210	166.0 (6.2)	167.5 (7.3)	153.9 (5.8)	153.0 (5.6)	<0.001	0.03
BMI[a] (kg/m^2)	2210	19.7 (17.7, 22.2)	21.3 (18.8, 24.2)	19.2 (17.3, 22.0)	22.9 (19.6, 25.7)	0.6	<0.001
Waist: hip ratio	2218	0.88 (0.1)	0.89 (0.1)	0.79 (0.1)	0.79 (0.1)	<0.001	<0.001
Fasting glucose [a](mmol/l)	2218	5.4 (5.1, 5.7)	5.5 (5.2, 5.8)	5.3 (5.0, 5.6)	5.4 (5.1, 5.8)	0.003	<0.001
30 min glucose[a] (mmol/l)	2216	8.1 (7.1, 9.2)	8.4 (7.4, 9.7)	7.9 (7.0, 9.0)	8.3 (7.4, 9.3)	0.09	<0.001
2 h glucose[a] (mmol/l)	2218	6.1 (5.2, 7.1)	6.3 (5.2, 7.4)	6.4 (5.5, 7.4)	6.6 (5.7, 7.7)	<0.001	0.002
Fasting insulin[a] (mIU/ml)	2218	35.2 (15.9, 58.7)	46.9 (22.1, 83.5)	20.7 (6.9, 40.0)	26.9 (11.7, 53.1)	<0.001	<0.001
30 min insulin[a] (mIU/ml)	2217	119.4 (67.6, 208.4)	211.8 (100.1, 376.1)	124.9 (61.4, 224.9)	178.7 (95.2, 334.0)	0.08	<0.001
2 h insulin[a] (mIU/ml)	2218	127.7 (75.2, 232.5)	201.5 (116.4, 344.0)	131.8 (67.6, 224.3)	183.5 (89.7, 330.5)	<0.001	<0.001
Insulin resistance (HOMA)[a]	2218	1.2 (0.5, 2.1)	1.7 (0.8, 3.0)	0.7 (0.2, 1.4)	1.0 (0.4, 1.9)	<0.001	<0.001
Insulin increment[a]	2216	9.4 3.6, 18.5)	13.7 (5.0, 27.8)	11.7 (5.2, 21.5)	15.9 (7.5, 32.0)	<0.001	<0.001
IGT [*n* (%)]	2156	112 (14%)	60 (17%)	126 (17%)	64 (22%)	0.05	0.02
DM [*n* (%)]	2218	16 (2%)	18 (5%)	18 (2%)	10 (3%)	0.7	0.01

Values are mean (SD) for normally distributed variables.

[a] Median (interquartile range) for skewed variables, or *n* (%) for categorical variables.

[b] For infancy, childhood and adolescence we have shown data for one timepoint only. Altogether 1622 subjects contributed infant data, 1893 childhood data and 1740 adolescent data.

[†] *p* for difference between sexes.

[††] *p* for difference between rural-born and urban-born subjects (derived using *t*-tests for continuous variables and Chi square tests for categorical variables).

Table 2 – Associations between measurements in early life and IGT/DM.

Early-life variable (Z-scores)	Unadjusted		Adjusted[a]	
	Odds ratio (95% CI)	*p* value	Odds ratio (95% CI)	*p* value
Parents				
Maternal BMI	1.01 (0.91, 1.13)	0.8	0.88 (0.79, 0.99)	0.03
Paternal BMI	1.00 (0.90, 1.11)	1.0	0.83 (0.73, 0.93)	0.002
Maternal height	0.88 (0.79, 0.98)	0.02	0.87 (0.78, 0.98)	0.02
Paternal height	0.97 (0.87, 1.08)	0.5	0.94 (0.84, 1.04)	0.2
Newborn				
Birthweight	0.97 (0.86, 1.07)	0.5	0.87 (0.78, 0.98)	0.02
Birth length	1.06 (0.96, 1.18)	0.3	0.98 (0.88, 1.10)	0.7
Ponderal index	0.93 (0.84, 1.04)	0.2	0.89 (0.79, 0.99)	0.04
Infancy				
Infant BMI	0.92 (0.81, 1.03)	0.2	0.93 (0.82, 1.06)	0.3
Infant length	1.07 (0.95, 1.21)	0.3	0.98 (0.87, 1.12)	0.8
Childhood				
Child BMI	0.81 (0.71, 0.92)	0.001	0.77 (0.67, 0.88)	<0.001
Child height	1.10 (0.98, 1.23)	0.1	0.94 (0.83, 1.07)	0.3
Adolescence				
Adolescent BMI	0.93 (0.82, 1.05)	0.2	0.73 (0.63, 0.84)	<0.001
Adolescent height	1.07 (0.95, 1.20)	0.3	0.91 (0.79, 1.04)	0.1
Changes in BMI Z-scores[b]				
Birth-adult BMI	1.38 (1.27, 1.50)	<0.001	1.31 (1.20, 1.43)	<0.001
Infancy-adult BMI	1.36 (1.24, 1.49)	<0.001	1.26 (1.15, 1.40)	<0.001
Child-adult BMI	1.56 (1.41, 1.71)	<0.001	1.47 (1.32, 1.63)	<0.001
Adolescent-adult BMI	1.66 (1.47, 1.87)	<0.001	1.56 (1.38, 1.77)	<0.001

All models were adjusted for age and sex.
Odds ratios measure the change in the odds of IGT/DM for a unit change in the predictor variable.
[a] *Further adjustments for*: current residence (urban/rural), adult BMI, waist/hip ratio, household possessions, alcohol consumption, tobacco use, physical activity score family history of diabetes, parity (women).
[b] *Adjustments*: adult life style factors excluding BMI and waist/hip ratio.

in Table 2 remained so (except for maternal height with IGT/DM, unadjusted: OR 0.87, $p = 0.1$; adjusted: OR 0.87, $p = 0.06$) and paternal BMI with IGT/DM, adjusted (OR 0.90, $p = 0.2$). The inverse associations of birthweight and ponderal index with IGT/DM were stronger in this limited sample, and the unadjusted associations, like the adjusted associations, were statistically significant (OR 0.77, $p = 0.003$ and OR 0.80, $p = 0.01$ for birthweight and ponderal index, respectively).

3.6.1. *Insulin resistance and measurements in earlier life*

Higher maternal and paternal BMI, taller paternal height, higher birthweight and ponderal index, and taller height in infancy, childhood and adolescence were all associated with increased insulin resistance, though these associations were diminished, and most became non-significant, after adjusting for adult lifestyle factors (Table 4). Similar to IGT/DM, lower childhood BMI and greater BMI gain between birth, infancy, childhood or adolescence and adulthood were associated with higher insulin resistance.

3.6.2. *Insulin secretion and measurements in earlier life*

Apart from positive associations between maternal and paternal BMI and insulin increment (neither significant after adjusting for adult BMI) there were no associations between parental size and adult insulin increment (Table 4). Longer birth length and taller height in childhood and adolescence was associated with higher insulin increment; but again, the effect was diminished after adjusting for adult lifestyle factors. Greater BMI gain between birth, infancy, childhood or adolescence and adulthood, was associated with higher insulin increment.

In the sub-set of men and women with data available at all timepoints, the statistically significant associations reported in Table 4 remained so, except those with birth size. Consistent with the findings for IGT/DM, these become more inverse. Thus the positive associations of birthweight and ponderal index with insulin resistance were no longer statistically significant (birthweight unadjusted: $B = 0.054$, $p = 0.09$; ponderal index unadjusted: $B = 0.047$, $p = 0.1$) and nor was the positive association between birth length and insulin increment (unadjusted $B = 0.025$, $p = 0.5$). There were now significant inverse associations of birthweight and ponderal index with insulin increment (birthweight adjusted: $B = -0.032$, $p = 0.01$ and ponderal index adjusted: $B = -0.081$, $p = 0.01$).

3.7. *Migration*

Place of birth was strongly related to current place of residence (rural or urban). Seventy-seven percent of subjects born in the rural area still lived there. Of subjects born in Vellore town, 84% still lived there and 13% had migrated to large cities (Bangalore or Chennai). Early life measurements for rural-born subjects who had migrated to a town or city did not differ from

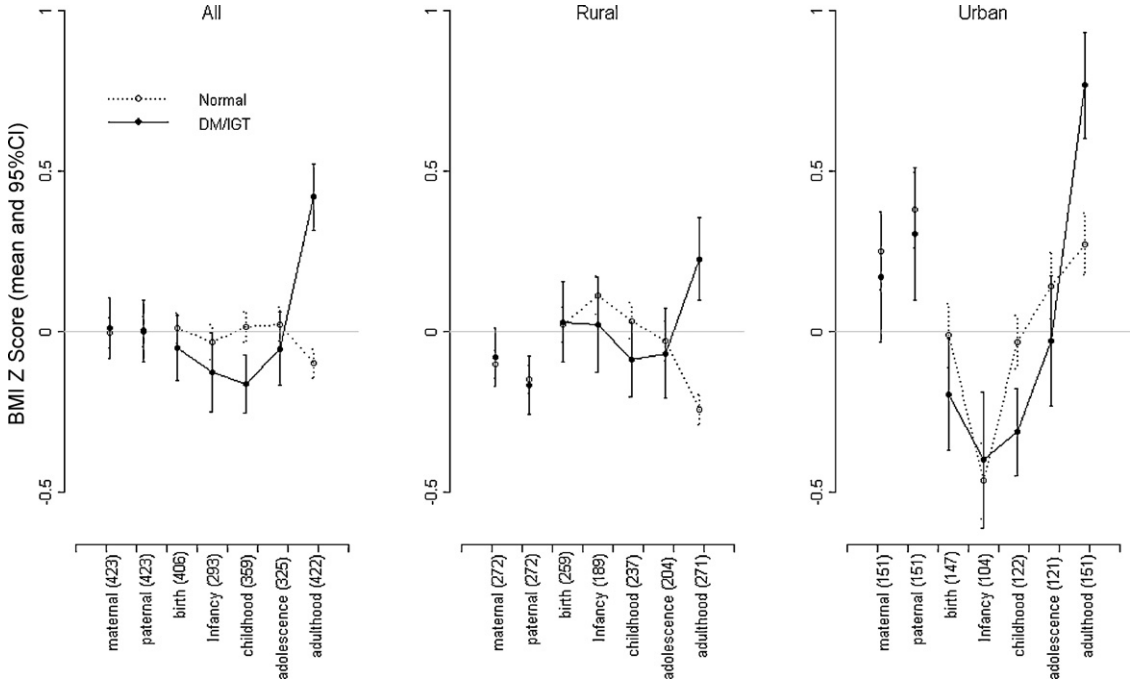

Fig. 1 – Mean Z-scores (95% CI) for maternal and paternal BMI, and the ponderal index at birth and BMI in infancy, childhood and adolescence of subjects with IGT or diabetes (closed circles and solid lines) or normal glucose tolerance (open circles and dashed lines) according to place of birth. The Z-score for the whole cohort is set at 0. All available data are used at each timepoint.

those who remained living in the rural area. Rural-born participants who had migrated to the urban area had a higher mean (SD) BMI than those who stayed in the rural area (men: 21.2 (2.9) vs. 19.9 (3.2); $p = < 0.001$; women: 21.0 (3.8) vs. 19.7 (3.7); $p = <0.001$), a greater increase in BMI Z-score between childhood and adulthood (men: 0.21 (1.2) vs. −0.26 (1.3); $p = <0.001$; women: −0.07 (1.3) vs. −0.27 (1.2); $p = 0.06$), and a higher prevalence of IGT/DM (men: 20.1% vs. 14.9%; $p = 0.09$; women: 23.6% vs. 17.3%; $p = 0.06$). However, among those currently living in a town or city, the prevalence of IGT/DM was similar in those who were rural-born (19.0% and 2.8%, respectively) to those born in Vellore town (18.8% and 4.3%) ($p = 0.5$).

4. Discussion

This large study of young rural and urban south Indian men and women from a prospective birth cohort showed that glucose intolerance and insulin resistance were associated with a lower BMI in childhood, followed by accelerated BMI gain relative to the whole cohort between birth, infancy, childhood or adolescence and adulthood. This pattern was observed despite the low BMI of this cohort by international standards, and even in thin rural subjects. Short maternal height, and after adjusting for adult BMI and lifestyle factors, lower maternal and paternal BMI, were associated with an increased risk of IGT/DM in the offspring. There were no direct

Table 3 – Prevalence of IGT or diabetes and odds ratios (95% CI) according to childhood and adult BMI.

Thirds of childhood BMI Z-score	Adult BMI (kg/m^2)						
	Percent (no.) of subjects with IGT/DM				Odds ratio (95% CI) for IGT/DM		
	<18.5	<23	≥23	Total	<18.5	<23	≥23
1	14.9 (255)	20.6 (243)	39.5 (129)	22.2 (627)	1.9 (0.9–3.7)	2.6 (1.3–5.0)	5.9 (2.9–11.8)
2	11.0 (209)	18.1 (254)	31.1 (167)	19.2 (630)	1.4 (0.7–2.8)	2.3 (1.2–4.4)	4.2 (2.1–8.2)
3	8.0 (162)	11.8 (289)	28.2 (177)	15.4 (628)	1.0 (referent)	1.5 (0.7–2.8)	3.8 (1.9–7.3)
Total	11.8 (626)	16.5 (786)	32.3 (473)	18.9 (1885)			

Odds ratios were calculated using a single logistic regression analysis, incorporating dummy variables for each child-adult BMI cell, and adjusting for age, sex, place of current residence (urban/rural), education, household possessions, alcohol consumption, tobacco use, physical activity score and family history of diabetes.

Table 4 – Associations between measurements in early life and insulin resistance and insulin increment.

Early-life variable (Z-scores)	Insulin resistance (Z-score)				Insulin increment (Z-score)			
	Unadjusted		Adjusted[a]		Unadjusted		Adjusted[a]	
	Regression coefficient (95% CI)	*p* value	Regression coefficient (95% CI)	*p* value	Regression coefficient (95% CI)	*p* value	Regression coefficient (95% CI)	*p* value
Parents								
Maternal BMI	0.053 (0.01, 0.09)	0.01	−0.001 (−0.04, 0.04)	0.9	0.048 (0.01, 0.09)	0.02	−0.009 (−0.05, 0.03)	0.7
Paternal BMI	0.054 (0.02, 0.09)	0.01	−0.016 (−0.06, 0.03)	0.5	0.084 (0.04, 0.12)	<0.001	0.016 (−0.03, 0.06)	0.5
Maternal height	−0.027 (−0.07, 0.01)	0.2	−0.026 (−0.06, 0.01)	0.2	−0.011 (−0.05, 0.03)	0.6	−0.012 (−0.05, 0.03)	0.6
Paternal height	0.065 (0.03, 0.10)	0.001	0.047 (0.01, 0.09)	0.02	0.037 (−0.004, 0.08)	0.08	0.023 (−0.02, 0.06)	0.3
Newborn								
Birthweight	0.055 (0.01, 0.10)	0.01	0.017 (−0.02, 0.06)	0.4	0.007 (−0.04, 0.05)	0.3	−0.032 (−0.07, 0.01)	0.1
Birth length	0.029 (−0.01, 0.07)	0.1	−0.004 (−0.04, 0.04)	0.8	0.049 (0.01, 0.09)	0.02	0.010 (−0.03, 0.05)	0.6
Ponderal index	0.047 (0.01, 0.09)	0.02	0.029 (−0.01, 0.07)	0.2	−0.019 (−0.06, 0.02)	0.4	−0.034 (−0.08, 0.01)	0.1
Infancy								
Infant BMI	−0.003 (−0.05, 0.04)	0.9	−0.009 (−0.05, 0.04)	0.7	−0.017 (−0.06, 0.03)	0.5	−0.005 (−0.05, 0.04)	0.8
Infant length	0.064 (0.02, 0.11)	0.01	0.036 (−0.01, 0.08)	0.1	0.044 (−0.004, 0.09)	0.07	0.008 (−0.04, 0.06)	0.7
Childhood								
Child BMI	−0.050(−0.10,−0.004)	0.04	−0.068 (−0.11, −0.02)	0.004	−0.030 (−0.08, 0.02)	0.2	−0.043 (−0.09, 0.01)	0.08
Child height	0.091 (0.05, 0.13)	<0.001	0.041 (−0.003, 0.09)	0.07	0.117 (0.07, 0.16)	<0.001	0.062 (0.02, 0.11)	0.01
Adolescence								
Adolescent BMI	0.062 (0.02, 0.11)	0.01	−0.012 (−0.06, 0.04)	0.6	0.047 (0.00, 0.09)	0.05	−0.032 (−0.08, 0.02)	0.2
Adolescent height	0.110 (0.07, 0.15)	<0.001	0.054 (0.01, 0.10)	0.02	0.102 (0.06, 0.15)	<0.001	0.029 (−0.02, 0.08)	0.2
Changes in BMI Z-scores[b]								
Birth-adult BMI	0.083 (0.05, 0.11)	<0.001	0.063 (0.03, 0.09)	<0.001	0.12 (0.09, 0.15)	<0.001	0.092 (0.06, 0.12)	<0.001
Infancy-adult BMI	0.096 (0.06, 0.13)	<0.001	0.082 (0.05, 0.12)	<0.001	0.12 (0.09, 0.16)	<0.001	0.086 (0.05, 0.12)	<0.001
Child-adult BMI	0.149 (0.12, 0.18)	<0.001	0.130 (0.09, 0.17)	<0.001	0.145 (0.11, 0.18)	<0.001	0.110 (0.07, 0.15)	<0.001
Adolescent-adult BMI	0.116 (0.07, 0.16)	<0.001	0.081 (0.04, 0.12)	<0.001	0.148 (0.11, 0.19)	<0.001	0.097 (0.05, 0.14)	<0.001

All models were adjusted for age and sex.

Linear regression coefficients measure number of SDs change in insulin resistance/insulin increment per SD change in the predictor variable.

[a] *Further adjustments for*: current residence (urban/rural), adult BMI, waist/hip ratio, household possessions, alcohol consumption, tobacco use, physical activity score family history of diabetes, parity (women).

[b] *Adjustments*: adult life style factors excluding BMI and waist/hip ratio.

associations between adult glucose intolerance and newborn size, or size in infancy, but after adjusting for adult BMI and lifestyle factors, smaller size at birth was associated with a higher risk of adult IGT/DM.

Strengths of our study were that this population-based cohort included rural and urban subjects, birth length was recorded in addition to birthweight, measurements made by trained personnel, and gestational ages and parental anthropometry. Adult measurements included plasma insulin profiles. The follow-up rate (21% of the original cohort) compared favourably with other longitudinal birth cohorts such as the Finnish cohort (9.5%) [15]. Weaknesses were that we had no data on maternal gestational diabetes (a risk factor for diabetes in the offspring), and that because follow-up occurred in phases, the children's age at adiposity rebound could not be determined (earlier rebound is a risk factor). Inevitably, the loss to follow-up means that the subjects studied were unrepresentative of the original cohort in some aspects. Differences in body size at birth and during infancy between subjects studied and not studied were small, but statistically significant. Firstborns were under-represented because primiparae often delivered in their mother's village outside the study area. Fetal and infant deaths would have been higher in smaller, less healthy babies. Missing data was not uniform at all timepoints, and was particularly marked in infancy. This is thought to be for two reasons: firstly, some mothers who delivered locally returned to their parental village for the immediate post-natal period and secondly, some mothers did not wish their new babies to be measured but were willing for them to be measured when they were older. Re-analysis of the data in the sub-set of participants with data at all timepoints led to an approximate halving of the sample size, but the main findings, that thinness at birth and during childhood followed by later BMI gain between early life and adulthood were associated with increased risk of developing IGT/DM and insulin resistance, were unchanged.

There are few previous data relating parental size to glucose intolerance in the offspring. Studies in various populations have reported higher insulin resistance in men and women whose mothers had a low BMI [16–18]. A study of men and women in Mysore, south India, showed an association of diabetes with high maternal weight [19]. After adjusting for potential confounding factors, we showed an association of lower maternal and paternal BMI with an increased risk of IGT/DM. Approximately one third of the mothers were undernourished according to BMI criteria (32.6% had a BMI less than 18.5 kg/m^2, indicative of chronic energy deficiency) [20]. Our data are, therefore, compatible with the hypothesis that adult glucose intolerance could be associated with maternal energy deficiency. The association with lower paternal BMI, however, could indicate a genetic mechanism linking parental BMI to IGT/DM risk in the offspring, or reflect the shared nutritional environment of fathers and mothers (fathers of lower nutritional status are likely to have wives of lower nutritional status). At these low levels of BMI, few women would have developed gestational diabetes, another well-established cause of Type 2 diabetes in the offspring. The prevalence of IGT/DM was increased in men and women born to shorter mothers, which may indicate an association with poor nutrition of the mother during her own fetal, childhood or adolescent growth.

A large number of birth cohort studies, mainly in high-income countries and white Caucasians, have shown that smaller size at birth is a risk factor for adult IGT and Type 2 diabetes [4,21,22]. The risk is greatest for people who became obese adults, and adjusting for adult BMI consistently strengthens the association with low birthweight [22,23]. The association with small size at birth appears to be inconsistent in developing countries and non-white-Caucasian populations [23]. Among four such studies published so far, IGT/DM was associated with high ponderal index at birth in Mysore, India [19], unrelated to birth size in Delhi, India [6], associated with low birthweight in China [24] and, after adjustment for adult BMI, associated with low birthweight in South Africa [25]. In the Vellore study, we found no direct association between size at birth and adult glucose intolerance in the main analysis, but there was an inverse association after adjustment for adult BMI and other factors. In the sub-set of participants with data at all timepoints, there was a direct inverse association between birthweight and IGT/DM. One possible reason for weaker associations in low-income countries could be high mortality among fetuses and infants, affecting lower birthweight individuals disproportionately, and reducing the power to observe associations with small birth size and disease in later life. Another possible reason is that the adult birth cohorts in low-income countries tend to be younger than their counterparts in high-income countries; the phenotype associated with small size at birth may become manifest only with increasing age [26].

There were no associations in our study between infant BMI and later IGT/DM. This contrasts with findings in the UK [27] and Finnish [28] cohorts, and with an urban Indian cohort (Delhi) [6], where lower infant BMI was associated with an increased risk of IGT/DM. A limitation of our data is that infant measurements were made only up to three months, whereas in these other cohorts they were made up to 1 year, and infant measurements were the ones most likely to be missing. In Vellore, urban infants were lighter and thinner than rural infants. This was perhaps related to past infant feeding practices (urban mothers tended to introduce formula-feeding earlier) and/or infection (urban families were more overcrowded).

Children who developed adult IGT/DM had a lower mean BMI than the cohort mean (Fig. 1) and accelerated BMI gain compared with the rest of the cohort in late childhood and/or adolescence. At any adult BMI, subjects who were thinner as children had a higher risk (Table 4). These data are consistent with findings in the Finland [28] and Delhi [6] cohorts. The underlying mechanisms are unknown, but may reflect associations between childhood BMI and adult body composition. Thinness at birth and in early childhood is associated with lower lean body mass, while rapid BMI gain after late childhood is associated predominantly with increased fat mass [29–32]. The associations of lower childhood BMI (possibly reflecting lower lean mass) and greater adult BMI gain (possibly reflecting greater fat gain) with higher adult insulin resistance are consistent with this (Table 4). Greater BMI gain between childhood or adolescence and adulthood was associated with higher insulin

increment. We do not interpret this as showing 'better' insulin secretion in these subjects; rather it is likely to reflect a response to the higher insulin resistance in individuals with this growth pattern.

It is not possible to say from this observational study whether it is childhood thinness, or later increase in BMI, or both, that increase the risk of IGT/diabetes. It is important for countries like India undergoing rapid nutritional transition to determine whether diabetes can be averted by optimising nutrition to avoid thinness in very early life and preventing excessive BMI gain in late childhood and adolescence.

5. Conflict of interest

The authors declare that there is no conflict of interest associated with this manuscript.

Acknowledgements

This study was supported by the British Heart Foundation and the Medical Research Council (UK). We thank the subjects who participated, the medical officers, field and laboratory staff, Abel Rajaratnam and R. Selvakumar for their kind co-operation. We also acknowledge the support of Sneha-India.

Funding: British Heart Foundation (RG/98001).

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